Remarks

Entry of this amendment and reconsideration of the subject application in view thereof are respectfully requested.

I. Claim Status

Claims 1-3 and 6-29 were pending in the application. Of these, claims 1-3, 10, 11 and 16-29 were withdrawn and claims 6-9 and 12-15 stood rejected. Claims 6 and 12 have been amended to clarify the invention. New claims 30-37 have been added. No new matter is added.

II. Specification

The specification has been objected because of a typographical error at page 11, line 2. The specification has been amended to correct obvious typographical errors. The specification has also been amended to claim the benefit of prior-filed provisional application.

III. Response to Rejections Under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 6-9 and 12-15 under 35 U.S.C. § 112, first paragraph, based on the assertion that the claim being broader than the enabling scope of the disclosure in the application as filed. The Examiner contends that while the specification is enabling only for an *in vitro* method of inhibiting the growth of cancer cells comprising administering an effective dose amount of a black tea extract comprising theaflavin-3-gallate and theaflavin-3'-gallate to cancerous cells, it does not reasonably provide enablement for a method for preventing or treating any or all diseases or conditions in an animal by modulating Cox-2 gene expression comprising administering to the animal the claim designated plant extract.

Without conceding the validity of this rejection and solely to expedite the prosecution of this application, Applicant has elected to strike "preventing" from claims 6 and 12. To the extent the Examiner maintains that the pending claims, as amended, are not enabled, Applicant respectfully disagrees.

First, Applicant respectfully submits that the presence of both anticipation rejection and enablement rejection in the Office Action against the same claims appears contradictory. For example, the Examiner found Yang et al., Phytochemicals and Phytopharmaceuticals, (2000), Editors Shahidi et al., AOCS Press, Champaign, Illinois, Chapter 17, pp 192-201 to be an anticipatory reference (discussed more fully below). This reference teaches that black tea extract inhibits cancer cell growth *in vivo*. To constitute an anticipatory reference, the prior art must contain an enabling disclosure. *Chester v. Miller*, 15 USPQ2d 1333 (Fed. Cir. 1990). If the Examiner believes that Yang enables the method of treating cancer using black tea extracts *in vivo*, then the enablement rejection must be withdrawn.

Further, the *in vitro* models used in the present invention are acceptable models for animals including humans with naturally occurring tumors and the *in vitro* data is sufficient to convince one of skill in the art of the asserted utility. Specifically, a person skilled in this art would recognize that the *in vitro* data in the specification as reasonably correlating to the claimed method and hence would have been able to practice the claimed invention by using only the teachings of the specification and the general knowledge available to such a person at the time that the application was filed. Particularly, in the context of theaflavin polyphenols and tea extracts, chemopreventive effects of these agents have been demonstrated in both *in vitro* and/or *in vivo* animal models of cancer of the skin, lung, esophagus, colon and mammary glands. See the specification at page 1, lines 18-25 and the prior art in this field that is already of record. See also, for example, the U.S. Patent No 6,410,061 (a copy of which is enclosed herewith) with claims to a method for treating cancer in a mammal using tea catechins based on cell culture data in the specification.

Given what is already known about theaflavins and their role in tumor inhibition, determining therapeutically effective amounts of TF2 is not an inventive activity. Those skilled in the art would have successfully determined the therapeutically effective amounts of TF2 sufficient for modulating COX-2 in an animal based on the *in vitro* data and the Examples in the application. Such findings would not place an undue burden on one skilled in the art, since it can be determined by routine and reasonable experimentation.

The Examiner cites Dermer (Bio/Technology, 1994, 12: 320) and Jain (Science, 1996, 271:1079-1080) references in support of the position that *in vitro* models do not reasonably correlate to *in vivo* treatment. Applicant respectfully disagrees with the Examiner's assertions and submits that these references are not reflective of the state of the art related to the use of therapeutic agents such as theaflavins or specific COX-2 inhibitors for animal and human applications based on the agents' *in vitro* anti-tumor activity. The Dremer article, published in 1994, is the author's personal opinion against the use of human tumor cell lines as a model system for cancer. The overwhelming evidence to date (including the prior art references of record), since the publication of the Dremer article, weigh against the Dremer's opinion. The NCI's drug development program that lead to commercialization of a number drugs is one such evidence. Likewise, the Jain article focuses on specific agents such as monoclonal antibodies, cytokines, antisense oligonucliotides, gene-targeting vectors, and genetically engineered cells and problems in overcoming physiological barriers to penetration of these agents into tumor tissue. The claimed method in the present patent application does not use the agents of the type referred to in the Jain reference. Specifically, the theaflavin polyphenols including theaflavin-3-gallate and theaflavin-3'-gallate are low molecular weight compounds and do not pose the penetration problems pointed out by Jain. See, the prior art of record.

The Examiner avers on page 6 of the Office Action that "effective treatments for preventing or treating such disease conditions are relatively rare, and may be unbelievable in the absence of supporting evidence." Applicant respectfully disagrees and submits that medical treatment of cancer is not such an inherently undelievable undertaking anymore nor it involves such implausible scientific principles as to be considered incredible. *In re Jolles*, 206 USPQ 885 (CCPA 1980). See also, *Ex parte Krepelka,* 231 USPQ 746 (Bd. Pat. App. & Int. 1986).

Accordingly, Applicant respectfully submits that the specification does provide sufficient disclosure to enable those skilled in the art to practice the full scope of the claims without undue experimentation. Reconsideration and withdrawal of this rejection are respectfully requested.

IV. Response to Rejections Under 35 U.S.C. §102

Claims 6-8 and 12-14 stood rejected under 35 U.S.C. §102(a) as anticipated by Yang et al., Phytochemicals and Phytopharmaceuticals, (2000), Editors Shahidi et al., AOCS Press, Champaign, Illinois, Chapter 17, pp 192-201 ("Yang" or "Yang et al. (U)"). Applicant respectfully traverses this rejection.

Yang teaches the use of black tea preparations for controlling the NNK-induced hyperprolifeartion of cells. Yang teaches that the preparations must contain theaflavins (i.e., theaflavin, theaflavin-3-gallate, theaflavin-3'-gallate and theaflavin-3, 3'-digallate) EGCG, EGC, ECG and EC. The Yang reference is also explicit in that the black tea preparation must contain all theaflavins.

The Examiner admits on page 10 of the Office Action that Yang does not expressly teach the claimed method but states that "the claimed functional effect to modulate Cox-2 gene expression is inherent to the method of administering the composition taught by Yang because cancer is associated with Cox-2 gene expression." This statement directly contradicts the Examiner's previous statement in the Office Action of November 18, 2002 (Paper No. 6). More specifically, on Page 3 of the Office Action of November 18, 2002, the Examiner stated that:

> In the instant case the two different groups are directed to two different inventions. For instance, the invention of Group II is directed to a method for inhibiting tumor cell growth in an animal comprising the administration of a claimed extract, whereas the invention of Group III is directed to a method for preventing or treating disease associated with Cox-2 gene expression in an animal comprising the administration of a claimed extract, wherein the disease can be either cancer, inflammation or arthritis. Cancer does not necessarily have to be associated with Cox-2 gene expression or tumor cell growth. Thus, it would be expected that the two different methods have different modes of operation, different functions, or different effects, since the methods are directed to the treatment or prevention of different disease conditions.

Applicant in its response to the Office Action of November 18, 2002, elected Group III claims without traverse. Given the admissions of record, the rejection based on inherent anticipation is improper. Further, inherent anticipation requires that the missing descriptive

material is "necessarily present," not merely probably or possibly present, in the prior art. *In re Robertson*, 49 USPQ2d 1949,(Fed. Cir. 1999). It is Examiner's burden to show that this element is "necessarily present," not merely or possibly present in the Yang reference.

Furthermore, the pending claims require the use of a sufficient amount of theaflavin-3-gallate and theaflavin-3'-gallate (together known as TF2) to modulate Cox-2 gene expression and to treat a disease or a condition in an animal. The prior art did not appreciate the fact that a sufficient amount of TF2 alone, without regard to various other theaflavins, is adequate to bring about Cox-2 modulation. While Yang discloses the use of an amount of theaflavins and other ingredients with one effect in mind, i.e., to decrease hyperproliferation of cells, the Applicant intends to use a sufficient amount of TF2 with another effect in mind, i.e., to cause differential effects of TF2 on the growth and death of cancer cells by differential modulation of Cox-2 gene expression. The specification, for example, at page 5, lines 21-26 teaches that:

> All three polyphenols were tested, TF-1, TF-2 and TF-3. Of the three compounds tested, only TF-2 significantly suppressed Cox-2 gene expression in Caco-2 cells. Effects were seen at doses of 50 to 100 μM TF-2. Despite their structural similarity, both TF-1 and TF-3 failed to affect Cox-2 gene expression.

In other words, though Yang discloses a theaflavin preparation to control cell proliferation, Yang did not appreciate the differential effect of TF2 on Cox-2 modulation. Yang's black tea preparation made with one effect in mind might not produce the desirable effect as to the Cox-2 modulation. Even "if it had done so under unusual conditions, accidental results, not intended and not appreciated, do not constitute anticipation." *Eiber Process Company v. Minnesota & Ontario Paper Company* 261 U.S. 45 (1923).

As such, the Examiner has not established a *prima facie* case of anticipation in support of the rejection of claims 6-8 and 12-14 based on the Yang reference. Therefore, in contrary to the Examiner's assertion, Yang does not anticipate claims 6-8 and 12-14 as it does not teach or disclose each and every limitation in each of these claims.

Claims 6-8 and 12-14 further stood rejected under 35 U.S.C. §102(b) as anticipated by DE19627344. Applicant respectfully traverses this rejection.

DE19627344 is an abstract. It makes a prophetic reference to the use of an extract of *Camellia sinensis* containing, epicatechin, epigallocatechin, epigallocatechin-3-gallate theaflavin, theaflavin-3-gallate, theaflavin-3'-gallate and theaflavin-3, 3'-digallate in chemotherapy. The abstract is explicit in that the composition must contain all theaflavins.

The Examiner admits on page 11 of the Office Action that DE19627344 does not expressly teach the claimed method but states that "the claimed functional effect to modulate Cox-2 gene expression is inherent to the method of administering the composition taught by DE19627344 because cancer is associated with Cox-2 gene expression." This statement directly contradicts the Examiner's previous statement in the Office Action of November 18, 2002 (Paper No. 6). More specifically, on Page 3 of the Office Action of November 18, 2002, the Examiner stated that:

> In the instant case the two different groups are directed to two different inventions. For instance, the invention of Group II is directed to a method for inhibiting tumor cell growth in an animal comprising the administration of a claimed extract, whereas the invention of Group III is directed to a method for preventing or treating disease associated with Cox-2 gene expression in an animal comprising the administration of a claimed extract, wherein the disease can be either cancer, inflammation or arthritis. Cancer does not necessarily have to be associated with Cox-2 gene expression or tumor cell growth. Thus, it would be expected that the two different methods have different modes of operation, different functions, or different effects, since the methods are directed to the treatment or prevention of different disease conditions.

Applicant, in its response to the Office Action of November 18, 2002, elected Group III claims without traverse. Given the admissions of record, the rejection based on inherent anticipation is improper. Further, inherent anticipation requires that the missing descriptive material is "necessarily present," not merely probably or possibly present, in the prior art. *In re Robertson*, 49 USPQ2d 1949,(Fed. Cir. 1999). It is Examiner's burden to show that this element is "necessarily present," not merely or possibly present in DE19627344.

Furthermore, the pending claims require the use of a sufficient amount of theaflavin-3-gallate and theaflavin-3'-gallate (together known as TF2) to modulate Cox-2 gene expression and to treat a disease or a condition in an animal. The prior art did not appreciate the fact that a sufficient amount of TF2 alone, without regard to various other theaflavins, is adequate to bring about Cox-2 modulation. While DE19627344 discloses the use of an amount of theaflavins and other ingredients with one effect in mind, i.e., to decrease hyperproliferation of cells, the Applicant intends to use a sufficient amount of TF2 with another effect in mind, i.e., to cause differential effects of TF2 on the growth and death of cancer cells by differential modulation of Cox-2 gene expression. The specification, for example, at page 5, lines 21-26 teaches that:

> All three polyphenols were tested, TF-1, TF-2 and TF-3. Of the three compounds tested, only TF-2 significantly suppressed Cox-2 gene expression in Caco-2 cells. Effects were seen at doses of 50 to 100 μM TF-2. Despite their structural similarity, both TF-1 and TF-3 failed to affect Cox-2 gene expression.

In other words, though DE19627344 discloses a preparation containing theaflavins to treat cancer cell proliferation, DE19627344 did not appreciate the differential effect of TF2 on Cox-2 modulation. DE19627344 preparation made with one effect in mind might not produce the desirable effect as to the Cox-2 modulation. Even "if it had done so under unusual conditions, accidental results, not intended and not appreciated, do not constitute anticipation." *Eiber Process Company v. Minnesota & Ontario Paper Company* 261 U.S. 45 (1923).

As such, the Examiner has not established a *prima facie* case of anticipation in support of the rejection of claims 6-8 and 12-14 based on DE19627344. Therefore, in contrary to the Examiner's assertion, DE19627344 does not anticipate claims 6-8 and 12-14 as it does not have an enabling disclosure or teach or disclose each and every limitation in each of these claims.

Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. §102 are respectfully requested.

V. Response to Rejections Under 35 U.S.C. §103

Claims 6-8 and 12-15 stood rejected under 35 U.S.C. §103(a) as anticipated by Yang et al. (U) and DE19627344 in view of Okuda et al (JP60025933) ("Okuda")and Xu et al. European J. of Cancer Prevention (1993). Vol. 2: 327-335 ("Xu"). Applicant respectfully traverses this rejection.

Contrary to what the Examiner appears to be urging, a *prima facie* obviousness has not been established in this case. A proper analysis under §103 requires, among other things, consideration of (1) whether the prior art would have suggested to those of ordinary skill in the art that they should carry out the claimed process; and (2) whether the prior art would also have revealed a reasonable expectation of success in carrying out the process. *See In re Vaeck,* 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). All the claim limitations must be suggested by the prior art. *In re Ochiai*, 37 USPQ 2d 1127 (Fed. Cir., 1995). A determination of obviousness must involve more than indiscriminate combination of the prior art; a suggestion or motivation to combine must exist. *Micro Chemical, Inc. v. Great Plains Chemical Co., Inc.,* 103 F.3d 1538, 41 USPQ2d 1238 (Fed. Cir. 1997), *cert. denied*, 117 S.Ct. 2516 (1997).

Yang and DE19627344 (abstract and its insufficient disclosure) are discussed above. Neither Yang nor DE19627344 discloses or suggests Cox-2 modulation by theaflavins, much less suggests the use of a sufficient amount of theaflavin-3-gallate and theaflavin-3'-gallate mixture to modulate the Cox-2 gene expression or how this can be done. Applicant notes that Yang and DE19627344 use compositions containing theaflavins for controlling cancer cell growth with no guidance, whatsoever, on how to successfully modulate the Cox-2 gene expression and treat the associated disease or a condition in an animal. Okuda and Xu do not cure the deficiencies in Yang and DE19627344.

The Examiner has not shown that one would be motivated to use a composition containing a sufficient amount of theaflavin-3-gallate and theaflavin-3'-gallate to modulate the Cox-2 gene expression in light of the teachings in Yang and DE19627344. Indeed, Yang and DE19627344, and a number of other prior art references that are of record (for example, Yang et al., (1997), Carcinogenesis, 18:2361-2365) suggest that extracts containing all theaflavins are

necessary for inhibiting growth of cancer cells. To the extent the prior art provides any motivation for adjusting the amount of a given theaflavin in a composition, it would be for theaflavin-3, 3'-digallate (also known as TF3). Recently, for example, Liang et al., (1999), Carcinogenesis 20:733-736, compared the effectiveness of TF1, TF2 and TF3 for the inhibition of carcinogenesis. They state on page 736 that "[t]he present studies clearly demonstrate that TF-3 may be the major active component that contributes to the antiproliferative activity in black tea. Moreover, TF-3 appears to be a better inhibitor of tyrosine receptor kinase than green tea polyphenol EGCG." Given these explicit prior art teachings, where is the motivation to use a composition containing a sufficient amount of theaflavin-3-gallate and theaflavin-3'-gallate to treat cancer?

If anything, given the reported effectiveness of TF3, there would be a disincentive for one of ordinary skill to focus on a composition containing sufficient amount of TF2 and orange peel extract to treat cancers associated the Cox-2 gene expression. Therefore, in contrary to the Examiner's assertion, there is no suggestion or motivation given to one skilled in the art to arrive at the claimed invention.

There must also be a reasonable expectation that the proposed combination or modification will be successful. There is no reasonable expectation that the methods of Yang and DE19627344, once modified to include the orange peel extract, can be successfully used to modulate Cox-2 gene expression and treat cancer.

In essence, there are no teachings in the cited art to suggest the desirability, and thus obviousness, of combining these references in a way that would lead to the claimed method. There is no reasonable expectation of success. Applicant respectfully submits that the cited combination of references is nothing more than an indiscriminate combination of prior art references in an attempt to reconstruct the claimed invention by hindsight.

While it may be argued, in light of Yang, that it would have been obvious to one skilled in the art to try [1] the claimed method, it would nevertheless be nonobvious to one of ordinary skill in the art because the differential effects of TF-2 was unexpected. Such an unexpected result, which is of a significant practical advantage, is an indication of nonobviousness. *In re Soni,* 34 USPQ2d 1684 (Fed. Cir. 1995).

Accordingly, Applicant respectfully submits that the Examiner has not established a *prima facie* case of obviousness of claims 6-9 and 12-15 because the cited references fail to meet the requirements for obviousness under 35 U.S.C. § 103(a). Reconsideration and withdrawal of the rejection are respectfully requested.

VI. Conclusion

Applicant believes this response to be a full and complete response to the Office Action. Accordingly, favorable reconsideration in view of this response and allowance of all of the pending claims are earnestly solicited.

Respectfully submitted,

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[1] Obvious to try is an improper ground for a §103 rejection. *In re Dow Chemical Co.* 5 USPQ2d 1529 (Fed Cir 1988)